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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication app ars on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003 and 15 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,36,38,40,44,46-51,53-58,62,64,65,69,71,72,74-77,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,36,38,40,44,46-51,53-58,62,64,65,69,71,72,74-77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/043,933* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *28* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

The request filed on 3/3/03 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/506,942 is acceptable and a RCE has been established. An action on the RCE follows.

Amendment to the Claims

In paper no. 25, applicant cancelled claims 33-35, 37, 43, 52, 59-61, 63, 66-68 and 78. Applicant states on page 11 of the response that claims 32, 44 and 74 have been amended. However, it is presumed that applicant intended to list claim 65 as currently amended instead of claim 74 because there is no marked up version present for claim 74, but there is one for claim 65 in paper no. 25 and the subsequent amendment to the claims submitted May 15, 2003. It is also noted that applicant included a copy of claim 73 in the claim summary document. However, this claim was cancelled in paper no. 16 submitted 4/2/2. Therefore, this claim is not pending and is not under consideration. The pending claims under consideration are: 32, 36, 38, 40, 44, 46-51, 53-58, 62, 64, 65, 69, 71, 72, 74-77, 79 and 80.

Claim Objections

Claims 32, 44 and 65 are objected to because of the following informalities:

Claims 32, 44 and 65 recite, "vector into which *are* inserted" (emphasis added). The recitation of "are" should be "is" since the vector is singular.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 recites the limitation "strain" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 74 recites the limitations "recombinant vaccinia virus", "Copenhagen" and "strain" in line 2. There is insufficient antecedent basis for these limitations in the claim.

It is suggested that applicant replace "strain" with "vector" to maintain consistency in the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 49 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to nononcogenic variants of E6 and E7. The specification has identified only one nononcogenic species of each, which are admittedly known in the art, see page 4, line 38 to page 5, line 6 and page 18, line 32 to page 19, line 8 of the specification. The claims do not require that the variants possess any particular distinguishing feature, biological activity, or conserved structure. Therefore, the claims are drawn to a genus of E6 and E7

variants that are defined only by a lack of oncogenic function. The courts have found that a definition by function alone "does not suffice, to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lily*, 119 F.3 at 1568, 43 USPQ2d at 1406.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing features identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation that the E6 and E7 variants be nononcogenic. There is no identification of any particular portion of the polypeptides that must be conserved in the claims or the specification. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nononcogenic E6 and E7 variants. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that

it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*; 18 USPQ2d 1016. Considering the extent of potential variation within the genus of nononcogenic E6 and E7 variants and the inability of one skilled in the art to predict which changes to the sequence will influence oncogenicity, it is concluded that the specification does not reasonably convey possession of the full genus of materials claimed.

Therefore, only a nononcogenic E6 variant consisting of a deletion spanning residues 111 to 115 and a nononcogenic E7 variant consisting of a deletion spanning residues 21 to 26, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 36, 38, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038).

Claim 32 is drawn to a composition consisting of an MVA vector into which is inserted DNA sequences expressing sequences that encode papillomavirus polypeptides E6, E7, L1 and L2 and a pharmaceutically acceptable carrier. Claim 36 is drawn to expressing the DNA sequences from one of the following promoters: TK, 7.5K, H5R and K1L. Claim 38 is drawn to the DNA sequences being inserted into at least one excision region, I-VI, within the MVA vector. Claims 53 and 54 are drawn to a method of treating and preventing dysplasia, cancer of the neck of the uterus, and papillomavirus infection by administering the composition of claim 32.

Lowy et al. teach a DNA molecule directing the expression of papillomavirus L1 and L2 polypeptides, see claims 16, 17 and column 4, line 62 to column 5, line 2 and lines 6-9. The expression of L1 and L2 produces papillomavirus-like particles are used in immunogenic compositions, see claims 1, 14 and column 5, lines 16-20. Lowy et al. teach that papillomavirus L1/L2 capsid proteins are prophylactic. Rabbits immunized with virus-like particles composed of L1/L2 are protected from subsequent infectious papillomavirus challenge, see column 2, lines 47-59. Lowy et al. suggest incorporating papillomavirus E6 or E7 into compositions to provide a therapeutic effect, see column 2, line 60 to column 3, line 16 and column 7, lines 35-61. Lowy et al. teach inducing neutralizing antibodies against E7 in rabbits by inoculation with L1/L2 papillomavirus-like particles, example 9 in column 14.

Although Lowy et al. specifically suggest a vaccinia vector to direct the expression of L1 and L2, see column 5, lines 7-9, Lowy et al. do not expressly teach expressing L1 and L2 from a vaccinia virus vector and vaccinia virus promoter, 7.5K.

Hagensee et al. teach expressing L1 and L2 papillomavirus proteins in a vaccinia virus with a 7.5K early promoter, see "Construction of recombinant vaccinia virus vectors" bridging pages 316-317.

One of ordinary skill in the art at the time the invention was made would have been motivated to express and administer the papillomavirus polypeptides of Lowy et al. in the vaccinia vector comprising the 7.5K vaccinia promoter of Hagensee et al. to eliminate the time-consuming step of expressing and harvesting the recombinant polypeptides from cell culture. One of ordinary skill in the art at the time the invention was made would have been motivated to express the polypeptides of Lowy et al. from the 7.5K vaccinia early promoter because the vaccinia promoter is obviously suitable to express papillomavirus polypeptides within a vaccinia virus vector, taught by Hagensee et al. in the result and discussion sections on pages 318-321. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing the polypeptides of Lowy et al. in the vaccinia vector of Hagensee et al. to elicit a protective immune response because Lowy et al. teach that presentation of conformational epitopes in L1/L2 is required for induction of immune reactivity, see column 3, lines 60-62 and column 6, lines 41-46, and Hagensee et al. teach that expression of L1 and L2 capsids from the vaccinia virus vector are indistinguishable from HPV-1 virions obtained from plantar warts, see the abstract, results and discussion sections. Therefore, the conformational epitopes required to be present in order to induce an immune response taught by Lowy et al. are present in the polypeptides expressed by the vaccinia virus vector of Hagensee et al.

Although Lowy et al. suggest incorporating papillomavirus E6 or E7 polypeptides into the composition and teach inducing neutralizing antibodies against E7 that is incorporated into

an L1/L2 capsid, neither Lowy et al. nor Hagensee et al. expressly teach incorporating papillomavirus E6 and E7 polypeptides into a composition.

Borysiewicz et al. teaches a Wyeth strain vaccinia virus encoding papillomavirus polypeptides E6 and E7 under the control of the 7.5K promoter to treat cervical cancer, see the abstract and "Vaccination with TA-HPV and patient monitoring" section on page 1524.

Galloway teaches that the early proteins, E6 and E7, from the papillomavirus are therapeutic in nature while the late proteins, L1 and L2 are prophylactic, see the abstract and the paragraph bridging pages 190 and 191. Galloway discusses prior art results of conferred protective immunity against papillomavirus infection in rabbits immunized with L1 or L2, see first full paragraph of column 2 on page 190. Galloway also teaches that L2 and E7 fusion proteins have reduced the number, severity, and duration of papillomavirus lesions and that E7 is found to protect mice from a syngeneic tumor in an MHC-restricted fashion, see the paragraph bridging pages 190-191.

One of skill in the art at the time of the invention would have been motivated to combine E6 and E7 of Borysiewicz et al. into the vaccinia vector of Hagensee et al. expressing the L1 and L2 proteins of Lowy et al. to treat and prevent papillomavirus infection in a host. One of skill in the art at the time of the invention would have had a reasonable expectation of success of producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Borysiewicz et al. and Galloway).

Although none of the references expressly teach treating and preventing dysplasia and cancer of the neck of the uterus, these conditions are notoriously well known in the art to be

attributed to papillomavirus infection. Therefore, since the references discuss treating and preventing papillomavirus infections, these more specific conditions caused by papillomaviruses would be included by the teachings of the prior art cited herein.

Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway do not teach the vaccinia virus strain MVA or incorporating the papillomavirus polypeptides into the recited excision regions or the K1L promoter.

Meyer et al. teach six major deletion sites in the wild-type vaccinia Ankara strain attenuate virus pathogenicity to MVA that are not essential to viral replication and, see the abstract and the results section on pages 1032-1034. In addition, Meyer et al. teach that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037.

Therefore, one of skill in the art at the time the invention was made would have been motivated to utilize the vaccinia MVA to express the papillomavirus polypeptides of Lowy et al. and Borysiewicz et al. or Galloway in a vaccine to treat papillomavirus infection because large insertion areas provided by the non-essential viral genome can be deleted without harming viral replication, taught by Meyer et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Hagensee et al. and Borysiewicz et al. teach expressing polypeptide genes in a vaccinia vector and Meyer et al. use a type of vaccinia virus, MVA, that allows the expression of large inserts. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 40, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

Claims 40, 57 and 58 require that the E6 and E7 polypeptides are nononcogenic variants. Specifically, E6 has amino acid residues 111-115 deleted and E7 has amino acid residues 21-26 deleted.

The teachings of Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. are discussed above. Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. do not teach nononcogenic E6 and E7 papillomavirus polypeptides with the recited deletions.

However, Crook et al. teach that an amino acid deletion of residues 111-115 in E6 reduces binding to p53, see Table 1 on page 549, Table 3 on page 550 and the paragraph bridging columns 1 and 2 on page 550. The teachings of Crook et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

Munger et al. teach a deletion of amino acid positions 21-24 of HPV-16 E7 abolishes binding to the retinoblastoma tumor suppressor gene. Munger et al. also teach mutagenesis at amino acid position number 26 also severely impairs binding to the retinoblastoma tumor suppressor gene, see the first full paragraph of the second column on page 4103. The teachings of Munger et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of E6 and E7. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Borysiewicz et al. and Galloway teach that E6 and E7 have ameliorative effects on papillomavirus infection and Crook et al. and Munger et al. teach E6 and E7 modifications to these papillomavirus polypeptides that reduce detrimental effects. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 44, 46, 48, 55, 56, 62 and 64 rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481).

Claims 44, 46 and 48 are drawn to a composition consisting of an MVA vector into which is inserted DNA sequences expressing sequences that encode papillomavirus polypeptides E6, E7, L1, L2, immunostimulatory molecule, IL-2, and a pharmaceutically acceptable carrier. Claim 62 is drawn to expressing the DNA sequences from one of the following promoters: TK, 7.5K, H5R and K1L. Claim 64 is drawn to the DNA sequences being inserted into at least one excision region, I-VI, in the MVA vector. Claims 55 and 56 are drawn to a method of treating and preventing dysplasia, cancer of the neck of the uterus, and papillomavirus infection by

administering the composition of claim 44. The difference between this composition and the composition of claims 32, 36, 38, 53 and 54 is the addition of IL-2 to the expression vector.

The teachings of Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. are discussed above. Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. do not teach expressing IL-2 in the papillomavirus composition.

Bubenik et al. demonstrate that the use of IL-2 as an adjuvant enhances the immunization effect in Syrian hamsters immunized with irradiated HPV 16-transformed tumor cells expressing E6 and E7, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the MVA vaccinia vector of Meyer et al. expressing prophylactic L1 and L2 proteins of Lowy et al. and Galloway, and the therapeutic E6 and E7 proteins of Borysiewicz et al. and Galloway, to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing IL-2 in the MVA vaccinia vector of Meyer et al. because Hagensee et al. and Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as IL-2 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 32, 36, 38, 44, 46, 48, 53-56, 62 and 64 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

Claims 49-51 require that the E6 and E7 polypeptides are nononcogenic variants. Specifically, E6 has amino acid residues 111-115 deleted and E7 has amino acid residues 21-26 deleted.

Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, Meyer et al. and Bubenik et al. above. None of the references teach nononcogenic E6 and E7 papillomavirus polypeptides with the recited deletions.

However, Crook et al. teach that an amino acid deletion of residues 111-115 in E6 reduces binding to p53, see Table 1 on page 549, Table 3 on page 550 and the paragraph bridging columns 1 and 2 on page 550. The teachings of Crook et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

Munger et al. teach a deletion of amino acid positions 21-24 of HPV-16 E7 abolishes binding to the retinoblastoma tumor suppressor gene. Munger et al. also teach mutagenesis at amino acid position number 26 also severely impairs binding to the retinoblastoma tumor suppressor gene, see the first full paragraph of the second column on page 4103. The teachings

of Munger et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Borysiewicz et al. and Galloway teach that E6 and E7 have ameliorative effects on papillomavirus infection and Crook et al. and Munger et al. teach E6 and E7 modifications to these papillomavirus polypeptides that reduce detrimental effects. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) as applied to claims 44, 46, 48, 55, 56, 62 and 64 above, and further in view of Baltz (American Journal of Health-System Pharmacy. 1995; 52: 2574-2585) and Gajewski (The Journal of Immunology. 1996; 156: 465-472).

Claims 47 and 48 are drawn to a composition consisting of an MVA vector into which is inserted DNA sequences expressing sequences that encode papillomavirus polypeptides E6, E7, L1, L2, immunostimulatory molecule, B7.1, and a pharmaceutically acceptable carrier.

The teachings of Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. are discussed above. Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, and Meyer et al. do not teach expressing B7.1 in the papillomavirus composition.

Baltz teaches co-administering an adjuvant, such as B7 molecules, with cancer antigens enhances the immune response to the antigen, see "Adjuvants" on page 2581. Baltz also reviews vaccine delivery by expressing antigen or cytokine genes into vaccinia virus, see "Recombinant DNA technology" bridging pages 2581-2582.

Baltz does not specifically teach B7.1.

Gajewski teaches that T cells require the participation of a "second signal" to secrete IL-2. This "second signal" capable of activating CD4+ and CD8+ T cells to secrete IL-2 is B7.1. B7.1 is necessary for the production of IL-2. Gajewski also teaches generation of tumor-specific CTL by transfecting B7.1, see the abstract and introduction sections on page 465 and the discussion section on page 470-471. Expression of B7.1 human tumor cells enables them to stimulate alloreactive CD8+ lymphocytes to produce their own IL-2, see the first paragraph of the discussion section on page 470.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate a B7 molecule of Baltz, such as B7.1, taught by Gajewski into the MVA vaccinia vector of Meyer et al. expressing prophylactic L1 and L2 proteins of Lowy et al. and Galloway, and the therapeutic E6 and E7 proteins of Borysiewicz et al. and Galloway, to augment the immune response to the papillomavirus polypeptides and stimulate the secretion of IL-2. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing B7.1 in the MVA vaccinia vector of Meyer et al. because

Hagensee et al. and Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. One of ordinary skill would further reason to expect success for expressing B7.1 of Gajewski in the MVA vector of Meyer et al. because Baltz teaches cancer vaccine delivery by expressing antigen or cytokine genes into vaccinia virus vector. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as B7.1 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481).

Claims 65, 72 and 74 are drawn to a composition consisting of an MVA vector into which is inserted DNA sequences that encode papillomavirus polypeptides E6, E7 and immunostimulatory molecule, IL-2, and a pharmaceutically acceptable carrier. Claim 69 is drawn to expressing the DNA sequences from one of the following promoters: TK, 7.5K, H5R and K1L. Claim 71 is drawn to the DNA sequences being inserted into at least one excision region, I-VI, in the MVA vector. Claims 79 and 80 are drawn to a method of treating and preventing dysplasia, cancer of the neck of the uterus, and papillomavirus infection by administering the composition of claim 65.

Borysiewicz et al. teaches a Wyeth strain vaccinia virus encoding papillomavirus polypeptides E6 and E7 under the control of the 7.5K promoter to treat cervical cancer, see the abstract and "Vaccination with TA-HPV and patient monitoring" section on page 1524.

Borysiewicz et al. do not teach utilizing IL-2.

Bubenik et al. demonstrate that the use of IL-2 as an adjuvant enhances the protective efficacy in Syrian hamsters immunized with irradiated HPV 16-transformed tumor cells expressing E6 and E7, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section bridging pages 479-480.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the vaccinia vector of Borysiewicz et al. expressing the therapeutic E6 and E7 proteins to augment the immune response to the papillomavirus polypeptides and to control the amounts of IL-2 expressed from the vaccinia vector. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for augmenting the immune response to E6 and E7 by expressing IL-2 from the vaccinia vector of Borysiewicz et al. because Bubenik et al. demonstrates an enhanced immune response against E6 and E7 by repeated injection with IL-2.

Although none of the references expressly teach treating and preventing dysplasia and cancer of the neck of the uterus, these conditions are notoriously well known to be attributed attributed to papillomavirus infection. Therefore, since the references discuss treating and preventing papillomavirus infections, these more specific conditions caused by papillomaviruses would be included by the teachings of the prior art cited herein.

Neither Borysiewicz et al. nor Bubenik et al. teach the vaccinia virus strain MVA or incorporating the papillomavirus polypeptides into the recited excision regions or the K1L promoter.

Meyer et al. teach six major deletion sites in the wild-type vaccinia Ankara strain attenuate virus pathogenicity to MVA that are not essential to viral replication and, see the abstract and the results section on page 1032-1034. In addition, Meyer et al. teach that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the MVA vaccinia vector of Meyer et al. expressing E6 and E7 proteins of Borysiewicz et al. to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing IL-2 in the MVA vaccinia vector of Meyer et al. because Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as IL-2 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8:

477-481) as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

Claims 75-77 require that the E6 and E7 polypeptides are nononcogenic variants. Specifically, E6 has amino acid residues 111-115 deleted and E7 has amino acid residues 21-26 deleted.

The teachings of Borysiewicz et al., Meyer et al., and Bubenik et al. are discussed above. The references do not teach do not teach nononcogenic E6 and E7 papillomavirus polypeptides with the recited deletions.

However, Crook et al. teach that an amino acid deletion of residues 111-115 in E6 reduces binding to p53, see Table 1 on page 549, Table 3 on page 550 and the paragraph bridging columns 1 and 2 on page 550. The teachings of Crook et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

Munger et al. teach a deletion of amino acid positions 21-24 of HPV-16 E7 abolishes binding to the retinoblastoma tumor suppressor gene. Munger et al. also teach mutagenesis at amino acid position number 26 also severely impairs binding to the retinoblastoma tumor suppressor gene, see the first full paragraph of the second column on page 4103. The teachings of Munger et al. are also admitted prior art in the paragraph bridging pages 8 and 9 of the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in

producing the claimed invention because Borysiewicz et al. and Galloway teach that E6 and E7 have ameliorative effects on papillomavirus infection and Crook et al. and Munger et al. teach E6 and E7 modifications to these papillomavirus polypeptides that reduce detrimental effects. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Response to Arguments

Applicant's arguments presented in paper no. 25 have been fully considered. However, some of the arguments are no longer relevant because of the different prior art applied against the instant claims due to the scope of amendment changes. Therefore, only arguments directed against the same prior art references cited herein will be addressed.

Applicant argues that Borysiewicz et al. do not teach or suggest the expression of L1 and L2 polypeptides in the same vaccinia vector.

Applicant's arguments have been fully considered, but are found unpersuasive because motivation to include prophylactic polypeptides, L1 and L2, is found in the combined teachings of Borysiewicz et al., Lowy et al. Hagensee et al. and Galloway.

One of skill in the art at the time of the invention would have been motivated to combine E6 and E7 of Borysiewicz et al. into the vaccinia vector of Hagensee et al. expressing the L1 and L2 proteins of Lowy et al. to treat and prevent papillomavirus infection in a host. One of skill in the art at the time of the invention would have had a reasonable expectation of success of producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Borysiewicz et al. and Galloway).

Applicant argues that the assertion of the Office action combining the prophylactic late and early therapeutic polypeptides in view of the teachings of Galloway are beyond the teaching in the art. Specifically, applicant asserts that Galloway does not suggest the possibility of combining the late and early polypeptides within the same composition because the reference uses the term "or" in hypothetical reference to vaccine compositions. Applicant asserts that the examiner's reason for combining early and late polypeptides into the same composition is found in the instant application.

Applicant's arguments have been carefully considered, but are found unpersuasive. The teachings of Galloway are based on a "Mini Review" of facts present in the prior art literature, not mere hypothesis, see the first line above the title of the reference. The conclusions of Galloway promoting a papillomavirus vaccine are based upon "the encouraging results with vaccines against animal PVs", see item (c) within the abstract. These results include protective efficacy demonstrated by several studies administering papillomavirus L1 and L2 polypeptides in various animal species, see the full paragraph in column 1 on page 190. The conclusions of Galloway concerning the therapeutic efficacy of papillomavirus polypeptides E6 and E7 are also based upon several experiments demonstrating tumor regression in animal models, see the paragraph bridging pages 190-191.

The protective efficacy of L1 and L2 polypeptides and the ameliorative properties of the E6 and E7 polypeptides are further evidenced by the prior art cited herein, see the teachings of Lowy et al. and Borysiewicz et al. Lowy et al. specifically suggest incorporating papillomavirus E6 or E7 into compositions to provide a therapeutic effect, see column 2, line 60 to column 3, line 16 and column 7, lines 35-61.

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have combined (E6, E7) and (L1, L2) polypeptides into the same composition in order to administer the composition to any individual, whether they had been previously infected with papillomavirus or not. The combined vaccine would possess the protective polypeptides, L1 and L2, to prevent infection in a host that has not encountered papillomavirus, as well as the therapeutic polypeptides, E6 and E7, to repress the growth of papillomavirus tumors present in an infected host. Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to combine polypeptides E6, E7 and L1, L2 into the same composition in order to administer the composition to any host, regardless of previous exposure or lack of previous exposure of papillomavirus by the host.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for treating and preventing papillomavirus infection in a host with a composition comprising E6, E7 and L1, L2 because Borysiewicz et al. and Galloway teach that E6 and E7 possess ameliorative properties and Lowy et al. and Galloway teach that L1 and L2 have prophylactic properties. One of ordinary skill in the art at the time the invention was made would have had further reason to expect success upon combining the early and late papillomavirus polypeptides because Lowy et al. not only suggest doing so, but also provide a working example combining L1, L2 and E7. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

With respect to the teachings of Gajewski, applicant argues that there is no teaching in Gajewski to express B7.1 and HPV polypeptides in an MVA vector. Applicant also asserts that Gajewski teaches away from the instant invention because Gajewski relies on in vitro stimulation of cells and provides no evidence that a recombinant vector could locally deliver an effective amount of B7.1 with the HPV polypeptides.

Applicant's arguments have been fully considered, but are found unpersuasive. If Gajewski taught an MVA vector expressing B7.1 and the instant HPV polypeptides, the reference would have been applicable under 35 USC 102. However, the teachings of Gajewski are only required to supply a teaching for the claim limitation reciting B7.1. This reference in combination with other teachings in the prior art reference would have rendered the invention prima facie obvious to one of ordinary skill in the art at the time the invention was made.

As discussed above, Baltz teaches co-administering an adjuvant, such as B7 molecules, with cancer antigens enhances the immune response to the antigen, see "Adjuvants" on page 2581. Baltz also reviews vaccine delivery by expressing antigen or cytokine genes into vaccinia virus, see "Recombinant DNA technology" bridging pages 2581-2582.

Neither Baltz nor Gajewski teach an MVA vector. However, Meyer et al. do. Meyer et al. teach six major deletion sites in the wild-type vaccinia Ankara strain attenuate virus pathogenicity to MVA that are not essential to viral replication and, see the abstract and the results section on page 1032-1034. In addition, Meyer et al. teach that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate a B7 molecule of Baltz, such as B7.1, taught by Gajewski into the MVA vaccinia vector of Meyer et al. expressing HPV papillomavirus polypeptides to augment the immune response to the papillomavirus polypeptides and stimulate the secretion of IL-2. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing B7.1 in the MVA vaccinia vector of Meyer et al. because Meyer et al. teach that the MVA vaccinia virus includes multiple insertion sites for heterologous inserts. One of ordinary skill would have had further reason to expect success for expressing B7.1 of Gajewski in the MVA vector of Meyer et al. because Baltz teaches cancer vaccine delivery by expressing antigen or cytokine genes into vaccinia virus vector. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as B7.1 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant argues that the teachings of Meyer et al. do not teach or suggest coexpressing papillomavirus polypeptides and an immunostimulatory molecule to treat HPV-associated lesions.

Applicant's arguments have been fully considered, but are found unpersuasive. If Meyer et al. taught an MVA vector expressing B7.1 and the instant HPV polypeptides, the reference would have been applicable under 35 USC 102. Lowy et al., Hagensee et al., Borysiewicz et al., Galloway, Bubenik et al., Baltz and Gajewski teach the limitations argued by applicant as lacking in Meyer et al. The combined teachings of Meyer et al. with other prior art references

cited discussed herein render the invention prima facie obvious to one of ordinary skill in the art. The three criteria of meeting the burden to establish obviousness have been met. First, the prior art cited against the instant application teaches all of the limitations in the claims. Second, a motivation to combine the references is found in the prior art. Third, the combination of references has been shown to produce the instant invention with a reasonable expectation of success at the time the invention was made.

With respect to the teachings of Crook et al. and Munger et al., applicant argues that the references fail to remedy the deficiencies of the prior art references cited in the previous rejection. However, this argument is not applicable to the instant rejections because the teachings of Munger et al. and Crook et al. are combined with other prior art citations which would have rendered the invention prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
May 29, 2003